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# Incidence of Microemboli and Correlation with Platelet Inhibition in Aneurysmal Flow Diversion

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## ABSTRACT

**SUMMARY:** Flow-diverting stents have been associated with embolic and hemorrhagic complications, but the rate of procedure-related microemboli is unknown. Using transcranial Doppler sonography, we measured the rate of microemboli in 23 patients treated with flow-diverting stents. Patients received preprocedural dual antiplatelet medications and intraprocedural heparinization. Point-of-care platelet reactivity testing was performed before the procedure, and nonresponders ( $>213$  P2Y<sub>12</sub>/ADP receptor reactivity units) received additional thienopyridine. Transcranial Doppler sonography was performed within 12–24 hours. Microemboli were detected in 3 patients (13%), 2 of whom were initially nonresponders. There was no association between the presence of microemboli and procedural or neurologic complications, aneurysm size, number of stents, or procedure time. Eight procedures (34.8%) required additional thienopyridine for inadequate platelet inhibition, and 3 required further treatment for persistent nonresponse to point-of-care platelet reactivity testing. There were 6 technical and 2 postoperative complications; none were associated with inadequate platelet inhibition or microemboli. The combination of routine point-of-care platelet reactivity testing and postprocedural microembolic monitoring may help identify patients at risk for thromboembolic complications after flow-diverting stents.

**ABBREVIATIONS:** FDS = flow-diverting stent; PRT = point-of-care platelet reactivity testing; PRU = P2Y<sub>12</sub>/adenosine diphosphate receptor reactivity units; TCD = transcranial Doppler sonography

The use of a flow-diverting stent (FDS) such as the Pipeline Embolization Device (Covidien/ev3, Irvine, California) in the treatment of unruptured, wide-neck, or fusiform intracranial aneurysms has had promising results.<sup>1,2</sup> However, reports of significant complications have arisen, such as delayed intraparenchymal hemorrhage in the arterial distribution of the reconstructed vascular segment.<sup>3,4</sup> The mechanism for this complication is hypothesized as thromboembolic<sup>5</sup> (possibly from foreign materials<sup>6</sup>) or hemodynamic<sup>4</sup> in nature, though the definitive mechanism is unknown.

Transcranial Doppler sonography (TCD) can be used to detect intra-arterial microembolic signals, a high frequency of which is thought to be predictive of embolic stroke.<sup>7</sup> TCD has been applied

to detect the rate of microemboli after endovascular aneurysm coiling to identify and treat patients at risk for thromboembolic complications.<sup>8,9</sup> To our knowledge, the rate of microemboli after aneurysm treatment with a FDS has not been reported.

Dual antiplatelet therapy with aspirin and a thienopyridine (commonly clopidogrel) is used to prevent endovascular thrombotic complications, especially in cerebrovascular stent placement.<sup>10</sup> However, up to 66% of patients undergoing stent placement show resistance to clopidogrel (“nonresponders”), and a lesser proportion are resistant to aspirin.<sup>11–14</sup> Antiplatelet resistance has been associated with thromboembolic complications,<sup>10,11</sup> though the inhibition threshold and timing of platelet testing is controversial,<sup>15,16</sup> as is the pharmacologic management of nonresponders.<sup>17,18</sup>

The purpose of this study was to describe the incidence of microemboli on routine postprocedural TCD monitoring after FDS placement in a series of consecutive patients with unruptured aneurysms and to analyze the interaction between microemboli and platelet inhibition.

## CASE SERIES


All patients with unruptured aneurysms treated between August 2011 and October 2012 with a FDS were included. Confidential chart review was performed to collect pertinent data, including

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 indicates article with supplemental on-line table

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the following: 1) patient demographics (sex, age, body weight at the time of the intervention); 2) aneurysm characteristics (location, dome and neck size if nonfusiform), procedural characteristics (number and length of FDSs, need for aneurysm coils, total fluoroscopy time, immediate angiographic outcome [and follow-up angiography if available]), periprocedural thromboembolic and technical complications; 3) medications administered before and during hospitalization (heparin, aspirin, clopidogrel, prasugrel, proton-pump inhibitors); and 4) diagnostic testing before and during hospitalization (point-of-care platelet reactivity testing [PRT], microembolic monitoring with TCD, neurologic examination on admission and discharge).

Patients were placed on a standardized anticoagulation protocol including at least 5 days of preprocedural dual antiplatelet medications (aspirin, 325 mg, and clopidogrel, 75 mg daily, except 1 patient who was switched from clopidogrel to prasugrel, 10 mg daily, due to gastrointestinal bleeding). PRT was performed 2–24 hours before the procedure by using the VerifyNow point-of-care platelet assay (Accumetrics, San Diego California). This test measures the degree of platelet inhibition by both aspirin (in aspirin reactivity units) and thienopyridines (in P2Y<sub>12</sub>/ADP receptor reactivity units [PRU])<sup>19</sup>; inadequate inhibition was defined as  $\geq 550$  aspirin reactivity units or  $> 213$  PRU.<sup>16</sup> Nonresponders between 214 and 224 PRU were given an additional 150 mg of clopidogrel; all other nonresponders were given 300–600 mg at the discretion of the attending neurointerventionalist. PRT was repeated in nonresponders within 24 hours of the procedure, and those with continued poor response were switched to prasugrel, 10 mg daily, after a 60-mg loading dose.

All interventional procedures were performed with the patient under general anesthesia. All patients were given intravenous heparin after diagnostic angiography but before the start of intervention, and activated clotting time testing was performed. Additional heparin boluses were given to maintain an activated clotting time of  $> 250$ . After an immediate postprocedural non-contrast head CT, patients were admitted to the intensive care unit for 24 hours with hourly vital signs and neurologic examinations.

Routine microembolic monitoring with TCD was performed by experienced vascular technicians on the first postprocedure day (12–24 hours after the procedure), by using an M-mode color-coded TCD oriented along the axis of the artery distal to the treated aneurysm (for carotid aneurysms, the ipsilateral MCA; in vertebral aneurysms, the ipsilateral posterior cerebral artery). TCD was performed for at least 20 minutes, and the number of microembolic signals was recorded. Those patients with detected microemboli remained in the intensive care unit and received additional anticoagulation (described below) and a TCD examination the following day.

Statistical significance was defined as a  $P$  value  $< .05$ , with Student  $t$  testing for quantitative and Fisher exact and  $\chi^2$  testing for qualitative variables.

Twenty-two patients underwent 23 consecutive FDS procedures for 25 aneurysms during the study period. Patient and aneurysm characteristics are shown in the On-line Table. One patient was treated twice due to incomplete aneurysm obliteration on follow-up imaging, and one had 3 distinct aneurysms treated

during the same procedure. All patients were treated with the Pipeline Embolization Device; 3 patients also received placement of a single coil in the aneurysm dome during the procedure, and 1 received multiple coils. All patients demonstrated marked stagnation of blood flow into the treated aneurysms on immediate posttreatment angiography. Of the 8 patients with follow-up imaging, 5 demonstrated complete aneurysm obliteration and 3 had residual filling for which 1 required additional FDS placement.

Six patients had intraprocedural complications (26.1%) including 1 proximal ICA dissection from a guide catheter (treated with a single dose of abciximab with immediate angiographic resolution), 1 femoral artery dissection requiring balloon angioplasty, 2 incidents of stent narrowing on postdeployment angiography requiring balloon angioplasty, and 1 each of distal stent dislodging and foreshortening requiring an additional stent. There were no clinical sequelae from these complications, and no microemboli were seen in any of the 6 patients. There were 2 postprocedural complications (8.7%). One patient displayed a small area of contrast extravasation ipsilateral to the treated aneurysm on routine postprocedural CT and remained asymptomatic. Another patient had transient diplopia, which resolved on the first postprocedure day. Both patients demonstrated adequate response on preprocedural PRT and no microemboli on postprocedural TCD. There were no permanent neurologic deficits in any patient.

No patient demonstrated aspirin resistance, but 8 patients (34.8%) demonstrated clopidogrel resistance on preprocedural PRT and received additional clopidogrel. Three remained nonresponders and were switched to prasugrel, with response on subsequent PRT. The average PRU for responders was significantly lower than that for nonresponders (128.0 versus 246.1,  $P < .001$ ). There was no significant difference between responders and nonresponders on all other variables, including age, body weight, aneurysm diameter, neck size, dome-to-neck ratio, total fluoroscopy time, or concurrent proton-pump inhibitor use.

Microemboli were detected by TCD in 3 patients (13%), 2 of whom were nonresponders on initial PRT but none of whom required prasugrel. Patient 4 had received a 600-mg bolus of clopidogrel before the procedure for inadequate platelet response (PRU 232). After TCD demonstrated 183 emboli/h, daily clopidogrel was increased to 150 mg and heparin infusion was started. An urgent diagnostic angiogram showed no thrombus, stenosis, or dissection. No further microemboli were noted on subsequent daily TCD, and the heparin was discontinued. The patient was discharged home on postprocedure day 3 with a PRU of 212. Patient 13 (who was also treated with a single coil in the aneurysm dome during the FDS procedure) was a responder on PRT (PRU 177). He had 15 emboli/h and received an additional 150-mg bolus of clopidogrel followed by 150 mg daily. Subsequent TCD demonstrated no microemboli, and the patient was discharged home with a PRU of 208. Patient 20 was a nonresponder on initial PRT (PRU 223) and received an additional 150 mg of clopidogrel before the procedure; TCD showed 6 emboli/h. She was placed on 150 mg of clopidogrel daily and was discharged the next day when TCD demonstrated 3 emboli/h; PRU were 186. There were no transient or permanent neurologic deficits among any patient with microemboli. There was no significant interaction be-

tween the presence of microemboli and platelet responder status ( $P = .27$ ).

## DISCUSSION

We have reported the incidence of thromboemboli as detected by postprocedural TCD following FDS treatment of unruptured aneurysms. We did not observe any major embolic or hemorrhagic complications, but 13% of procedures resulted in detectable microemboli and the patients received additional anticoagulation. Thromboembolic complication rates of up to 9.3% were reported in large series using the Pipeline FDS,<sup>2,5,20</sup> while the reported rate in stent-assisted aneurysm coiling was 2.0%–7.4%.<sup>21–23</sup>

Embolic phenomena are common after aneurysm coiling, and asymptomatic DWI abnormalities were found in 61%–69% of patients on postprocedural MR imaging.<sup>24,25</sup> A comparison of single and dual antiplatelet agents during aneurysm coiling (including balloon or stent assistance, but not FDS) found no difference between regimens for symptomatic ischemic complications and asymptomatic postprocedural DWI abnormalities, except in the case of wide-neck aneurysms.<sup>26</sup> However, a reduction in the frequency and size of DWI lesions was found in patients receiving larger heparin boluses during aneurysm coiling.<sup>27</sup>

Microemboli detected with TCD are associated with stroke, especially at a rate of >10/h, in carotid disease<sup>28</sup> and aneurysm coiling in high-risk patients.<sup>9</sup> Schubert et al<sup>8</sup> used routine postprocedural TCD embolic monitoring in 123 aneurysm coiling procedures (not including FDS) and found microemboli in 8.1% of patients during monitoring between 12 and 24 hours postprocedure. Continuous heparinization lowered neurologic deficits and embolic counts significantly; embolic counts trended lower with clopidogrel use.

We found a higher rate of microemboli (13%) after FDS. Our study lacked the power to draw statistical conclusions regarding microembolic risk factors, but 2 of the 3 patients were nonresponders to clopidogrel before the procedure. We found no other demographic, anatomic, or procedural characteristics associated with emboli.

Platelet aggregation on the stent wall, exacerbated by a variable response to platelet inhibition, has been implicated in embolic complications from stent-placement procedures.<sup>11–13,29</sup> Rates of thrombosis-related complications among coronary interventional and neuroendovascular procedures appear higher in nonresponders.<sup>10,11,30</sup> A prospective study of patients undergoing coronary intervention found that the lack of response to antiplatelet agents was an independent risk factor for asymptomatic DWI lesions on postprocedural MR imaging.<sup>31</sup>

Antiplatelet resistance appears to be multifactorial. Genetic polymorphisms have been found in 25%–64% of patients with cardiovascular disease.<sup>17,30</sup> Genetic testing is not commercially available, so the genetic polymorphisms of our patient population are unknown. An association between the use of proton-pump inhibitors and reduced clopidogrel has been reported<sup>32</sup> but did not lead to increased rates of thrombosis in a large randomized trial.<sup>33</sup> We did not find a correlation between proton-pump inhibitor use and clopidogrel resistance or microemboli, though only 5 of 23 patients received proton-pump inhibitors. Finally,

higher body weight has been associated with clopidogrel resistance.<sup>34</sup> Our study did not find a significant difference between body weights of responders and nonresponders, though there was a trend toward clopidogrel resistance ( $P = .07$ ).

The periprocedural management of patients with inadequate platelet inhibition is controversial, and most neuroendovascular guidelines are extrapolated from cardiovascular studies. A meta-analysis<sup>35</sup> comparing loading doses of 300 or 600 mg of clopidogrel found fewer cardiovascular complications with a higher dose, but a large randomized trial showed no effect on thrombosis-related complications in nonresponders.<sup>36</sup> Some authors suggest a dose-dependent strategy based on genotype<sup>17</sup> or switching to prasugrel,<sup>37</sup> as we did if follow-up PRT inhibition was inadequate.

The implications of microemboli after FDS placement are not well understood. Delayed intraparenchymal hemorrhage in the same arterial distribution as a recently placed (1–14 days) FDS is a complication unique to FDSs compared with other stent-assisted neuroendovascular procedures, at rates of up to 8.5%.<sup>3</sup> Thromboemboli have been implicated in the pathogenesis of this complication,<sup>5</sup> which may be due to increased coverage or rigidity of FDS devices, procedural complexity, altered downstream hemodynamics, destabilization of the aneurysm wall, or a combination of factors.

Some authors have hypothesized that postprocedural thromboemboli can produce silent ischemic events with subsequent hemorrhagic conversion. A recent postmortem report of 3 patients with such delayed hemorrhages found foreign body embolic material obstructing the vessels in and around the hemorrhage; these materials were not found elsewhere in the brain.<sup>6</sup> The origin of this material is unclear but could be related to the FDS or equipment used in its deployment.

Postprocedural aneurysm rupture is another rare complication unique to FDSs.<sup>38</sup> Hemodynamic changes induced by FDS placement have been implicated in recent computational fluid dynamics studies.<sup>39</sup> Histologic examination of the wall of aneurysms with delayed rupture demonstrated necrosis in several studies,<sup>38,40</sup> suggesting that intra-aneurysmal thrombosis after FDS placement leads to excessive platelet degranulation and aneurysm wall degradation. Given the varied presentation of hemorrhagic complications reported after treatment with a FDS, the authors suspect that the etiologies may include thromboemboli.

This report has several limitations. First, this was an observational study with a small cohort ( $n = 23$ ) of almost exclusively anterior circulation aneurysms, without a control group. Second, reports are conflicting regarding the appropriate cutoff to define poor platelet inhibition. We used the results of Godino et al<sup>16</sup> (>213 PRU) because they correlated well with flow cytometry, considered one of the criterion standard platelet response tests. However, other studies have used higher values<sup>36</sup> or instead considered the percentage of PRU compared with a baseline value.<sup>12,34</sup> Third, our anticoagulation protocol for the management of nonresponders has not been prospectively validated. Finally, microemboli detection by using TCD did not begin until 12–24 hours after the procedure; immediate postprocedural asymptomatic microemboli may have been missed.



## CONCLUSIONS

We observed a 13% rate of microemboli by using routine post-procedural TCD monitoring after FDS treatment of unruptured aneurysms in our small cohort. Overall, 34.8% of patients were nonresponders according to preprocedural PRT, including 2 of the 3 patients with microemboli. A combined approach of preprocedural PRT and postprocedural embolic monitoring may identify patients at risk of thromboembolic complications after treatment with a FDS.

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